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Stochastic modeling of near-field exposure to parabens in personal care products

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Abstract

Exposure assessment is a key step in determining risks to chemicals in consumer goods including personal care products (PCPs). Exposure models can be used to estimate exposures to chemicals in the absence of biomonitoring data and as tools in chemical risk prioritization and screening. We apply a PCP exposure model based on the product intake fraction (PiF), which is defined as the fraction of chemical in a product that is taken in by the exposed population, to estimate chemical intake based on physicochemical properties and PCP usage characteristics. The PiF can be used to estimate route and pathway specific exposures during both the use- and disposal-stages of a product. As a case study, we stochastically quantified population level exposures to parabens in PCPs, and compared estimates to biomarker values. We estimated exposure based on the usage of PCPs in the female US population, taking into account population variability, product usage characteristics, paraben occurrence in PCPs, and the PiF. Intakes were converted to urine levels and compared to NHANES (National Health and Nutrition Examination Survey) biomonitoring data. Results suggest that for parabens, chemical exposure during product use is substantially larger than environmentally mediated exposure after product disposal. Modeled urine concentrations reflect well the NHANES variation of three orders of magnitude across parabens for the 50^{th}, 75^{th}, 90^{th}, and 95^{th} percentiles and were generally in good agreement with measurements, when taking uncertainty into account. This study presents an approach to estimate multi-pathway exposure to chemicals in PCPs and can be used as a tool within exposure based screening of chemicals as well in higher tier exposure estimates.

Keywords: exposure modeling, dermal exposure, inhalation exposure, multi-media studies, personal exposure, population based studies

1. Introduction

In order to inform risk assessment of chemicals in cosmetics and personal care products (PCPs) an understanding of individual and population level exposure is required.[1,2] The need for exposure estimates based on various chemical uses is highlighted by the recent advances in high-throughput exposure models for chemical prioritization[3,4] which can also be combined with high-throughput toxicity estimates to inform risk.[5,6] Historically, these modeling efforts have focused on far-field environmentally mediated exposures and less on near-field pathway exposures occurring indoors and during product use.[3,7] Usage of PCPs has been shown to be well correlated with exposure[8,9] and use-phase exposure has been estimated to be greater than environmentally mediated exposure.[10,11] Modeling techniques can be used to estimate near-field and use-phase exposures to chemicals in PCPs and can be used to further enhance chemical prioritization methods for chemicals in consumer products.[6]

Several calculations have been developed to estimate chemical intake via PCP use and are based on multiplicative models[1,2,12] using a set skin permeation fraction often derived from the literature and do not necessarily take exposure duration (e.g. rinse-off versus leave-on into account).[1] On the other hand, models have been developed to estimate the skin permeation coefficient of a chemical[13,14] and chemical uptake into the skin.[15,16] Skin permeation models provide the advantage that they can be applied to chemicals based on physicochemical properties (i.e. octanol-water partition coefficient, K_{ow}, and molecular weight) thereby lending themselves to computationally based calculations rather than relying on data from the literature which is not conducive to multiple chemical calculations. Furthermore, models used to estimate exposure to chemicals applied dermally vary in mathematical complexity, for example by assuming only one chemical fate pathway (i.e. dermal uptake),[15] or only providing complex numerical solutions.[16]

Modeling frameworks are currently being developed to combine dermal uptake with the concept of the *product intake fraction*, PiF, defined as the fraction of the chemical in a product that is eventually taken in by the exposed individual(s)/population.[17] These models can be applied to predict chemical intake via several different pathways such as dermal uptake, inhalation intake and gaseous dermal uptake of volatilized chemicals, and to environmentally mediated exposure after product disposal. The advantage of this multi-pathway approach is that the relative contribution of each pathway can be estimated and does not assume that exposure only occurs via dermal uptake of product applied to the skin and allows for comparison between use-phase and disposal-phase exposures.

Such models, however, have yet to be evaluated on a population level using for example, biomarker data. Additionally, exposure is often estimated based on the usage of a single product rather than an aggregate analysis taking into account usage of multiple products containing a given chemical[1,2,15], which may underestimate a consumer's entire exposure for chemicals found in multiple product types. Cowan-Ellsberry and Robison[1] and Gosens et al.[2] present aggregate exposure estimates for parabens in PCPs, however their estimates do not use a skin permeation model nor are their estimates validated against biomarker data. Delmaar et al.[15] estimated aggregate exposure to diethyl phthalate using a skin permeation model, however they only consider the dermal exposure pathway. The application of a multi-pathway exposure model to estimate cosmetic intake has not been validated on a population level nor applied across multiple product types to yield aggregate exposure estimates. To address this gap, the product intake fraction concept would need to be adapted to several PCPs and validated against population level data. Evaluation of a PCP exposure model using data rich chemicals will build further

confidence in these techniques such that they can be incorporated into Tier 1 exposure and risk screening approaches and used on a broader range of chemicals.

In this paper, we apply the PiF concept to model chemical intake due to PCP usage using parabens as a case study. In order to compare the estimated intakes to population-based biomonitoring data we probabilistically combined the PiF calculations with aggregate exposure considerations to capture population variability, focusing on a class of widely used chemicals. This type of analysis is referred to as a Tier 2 probabilistic exposure estimate[18] and is more detailed than point estimates often used in screening approaches (Tier 1).[6] Parabens are commonly used in PCPs and cosmetics as preservatives, are readily absorbed into the skin,[19] are detectable in urine,[20] and thereby provide a good PCP exposure case study. Urinary biomarker data is available for the US population from NHANES (National Health and Nutrition Examination Survey)[21] where parabens have been detected in ~99% of the population.[22] Additionally, parabens are suspected endocrine disruptors[23,24] and these exposure calculations provide a basis for informing risk when combined with toxicity, bioactivity, or allowable dose data.[17] This study therefore aims to:

1. Estimate and contrast modeled *product intake fraction* for various exposure pathways (including near and far-field exposures) for parabens in a variety of PCPs and cosmetics while accounting for both chemical specific properties and product use characteristics.
2. Develop a stochastic method to produce population distributions of exposure resulting from the usage of multiple PCPs.
3. Evaluate the stochastic method by comparing its predictions with NHANES urine concentrations at different percentiles (50^{th} to 95^{th}) of exposure in the US population.

2. Methods

We used four common parabens methyl, ethyl, propyl, and butyl paraben (MeP, EtP, PrP, BuP, respectively) and eleven commonly used personal care products (PCPs) as a case study. We included rinse-off products (shampoo, conditioner, facial cleanser, body wash) and leave-on products (body lotion, face cream, night cream, deodorant, foundation, eye shadow, and lipstick). We studied the U.S. female population due to the availability of urine biomarker data[21] and the significantly higher exposure of the female versus male population to parabens.[22]

2.1 Product Intake Fraction

We used the product intake fraction (PiF) metric to assess the fraction of parabens in products that humans are exposed to a) during product use and b) via subsequent environmental emissions after product use. The PiF is defined as the ratio of the amount of chemical in a product that is taken in by humans and the amount of chemical contained in that product and depends on physicochemical properties as well as product use characteristics.[17] Once a product is applied we assumed that it can undergo the following pathways: direct dermal uptake into the skin, volatilization to air, and washed down-the-drain after the product is rinsed off. Following from these pathways, we calculated a PiF for each of the following exposure pathways: dermal uptake of chemical in an aqueous product ($PiF^{\mathrm{derm,aq}}$), inhalation of chemical from the volatilized product (PiF^{inh}), gaseous dermal uptake of chemical from the volatilized product ($PiF^{\mathrm{derm,gas}}$), and environmentally mediated chemical intake due to disposal after product use (PiF^{disp}), for each paraben and each PCP type.

The expression for dermal uptake of chemicals in aqueous products into the skin ($PiF^{\mathrm{derm,aq}}$) is based on a two-compartment mass balance between product and skin and yields the following solution (see Table S1 in Supplementary Information (SI)):

$$PiF^{\mathrm{derm,aq}} = \frac{k_{\mathrm{ps}}}{k_{\mathrm{ps}} + k_{\mathrm{pa}}}\left(1 - \mathrm{e}^{-(k_{\mathrm{ps}}+k_{\mathrm{pa}})t}\right) \quad (1)$$

where k_{ps} (h^{-1}) and k_{pa} (h^{-1}) are the product-skin and product-air transfer rates, respectively and *t* (h) is the exposure time, that is the duration that the product stays on the skin before being washed-off. The transfer rates k_{ps} and k_{pa} are both functions of the thickness of product on the skin, in addition to chemical specific parameters such as the aqueous skin permeation coefficient, K_p^{aq} (cm h^{-1}) and the air-water partition coefficient (K_{aw}) respectively. Expressions for the intake of volatilized chemical via inhalation (PiF^{inh}) and gaseous dermal uptake ($PiF^{derm,gas}$) are given in SI, Table S1, and are summed with $PiF^{derm,aq}$ to constitute the total use-stage, PiF^{use}, via these exposure routes.

The PiF associated with product disposal, PiF^{disp} (SI, Table S1), was modeled as the fraction of chemical not taken in during use and subsequently washed down the drain into a waste water treatment plant (WWTP) and then released to environmental compartments (air, water, soil). The subsequent environmental intake fractions (iF) were calculated using the USEtox model.[25] Finally, a chemical and product specific PiF^{tot} can be defined as the sum of chemical intakes via all considered pathways (i.e., $PiF^{derm,aq}$, $PiF^{derm,gas}$, PiF^{inh}, PiF^{disp}) and represents the total chemical intake via all exposure routes. More details on the calculation of the various pathway and route specific PiFs can be found in the SI (Section S1).

We note that some personal care products may also lead to non-dietary ingestion exposure, for example mouthwash and toothpaste, however these products are not reported to contain parabens[12,26] and were thus not included in the model. An ingestion PiF can be readily incorporated into this modeling framework and can take the value of the fraction of product that is ingested per product use. For example, for toothpaste Bremmer et al.[27] used measured values to estimate a toothpaste ingestion fraction. We did not include an ingested fraction for lipstick as

the resulting median $PiF^{derm,aq}$ was already larger than 50% for all parabens, and previously assumed fixed ingestion fractions for lipstick can vary greatly (e.g. from 0.1-100%).[4,27]

2.2 Total daily intake

The PiF^{tot} can then be used to calculate daily intake for a given chemical in a product and can be summed across several different products (p) to calculate an aggregate chemical intake, I (mg kg^{-1} d^{-1}) as

$$I = \frac{\sum_{p} PiF_{p}^{tot} M_{p} f_{p}}{BW} \quad (2)$$

where M_p (mg d^{-1}), f_p, and BW (kg) are the daily mass of product applied, fraction of chemical in the product, and body weight, respectively.

2.3 Monte Carlo Analysis, Model Parameterization, and Aggregate Exposure

Several of the parameters used as input to model the intake of chemicals in PCPs are subject to population variability, i.e. can have a range of possible values depending on individual characteristics and behavior within the studied population. We used Monte Carlo (MC) analysis to incorporate this population variability into our intake calculations. The parameters included in the analysis as well as their distributions are listed in SI, Table S5. The MC analysis was carried out for each product and chemical combination by generating 10^5 random values for each input parameter from the given probability distribution and using these values to calculate an intake distribution. Thus in total for four parabens in 11 PCPs yields 44 calculated intake distributions. We note that the MC analysis considered variables to be independent and potential impacts of variable correlations were not assessed.

Several key parameters dictate the calculated PiF and intake for a given product-chemical combination and include the aqueous skin permeation coefficient, K_p^{aq}, the daily amount of

product used, M_p, and the fraction of chemical in the product, f_p (Eq. 2). We collected empirical values of K_p^{aq} for parabens conducted in different media such as an aqueous solution or with an added alcohol and based the input distribution on these values[28–33] (Table 1 and S3).

For the daily mass of product usage, we used distribution data from Loretz et al.[34–36] as these data pertain specifically to the U.S. female population and detailed information on distributions were available for the MC analysis. Generally, there is limited information available on the chemical composition of consumer products, including PCPs.[26] We collected fraction paraben content information from various sources[1,12,37] and aggregated this data into a uniform distribution (see SI Section S3 for details) with example values for shampoo and body lotion in Table 1.

Up until this point, all calculations were described for a given product-chemical combination used by the exposed population and do not account for the population with zero exposure. In reality, different consumers use different combinations of products, with some products containing paraben(s) and some not. Thus, in order to calculate aggregate exposure to PCPs, the probability of occurrence of a given chemical within a PCP (percentage of products with a given paraben) and the probability of product use (percentage of population that uses a given product) need to be taken into account[1] (Figure S4, SI). The initial distributions created for the chemical intake of the exposed population are thus adjusted for the unexposed population by adding the appropriate amount of zeros representing non-exposure to the 44 distributions of 10^5 values calculated for the exposed population.

2.4 Product co-use

To calculate the population exposure to parabens, the co-use of PCPs should also be taken into account. For a given paraben there are eleven intake distributions representing each product

with several entries representing zero exposure based on the exposure probability; we randomly permeated these distributions and then summed intake across products. This yields a single aggregated intake distribution for each paraben (four distributions in total) with each entry representing a random sum of product intake percentiles with some products having zero intakes. We note that paraben exposure can occur via other media such as food and dust,[19,38,39] however these media have been estimated to contribute substantially less to exposure levels when compared to those occurring from direct PCP use.[1,12,39]

To demonstrate the potential usage of the PiF for risk screening, we also applied Eq. (2) using the 99th percentiles for all values (except body weight, which was set to a constant 75 kg) and added intake across all eleven products to yield a high-end usage scenario. This intake estimate represents a user who uses all eleven products which all contain parabens, and does not take into account any of the exposure adjustments described above. This intends to represent the very high-end of potential exposure, within the intended use of PCPs.

2.5 Converting external intake into urine concentrations

The inclusion of the MC analysis to produce intake distributions also allows for comparison to NHANES biomonitoring data which is in the form of population percentiles.[21] In order to compare modeled intakes to biomonitoring data, we converted the dose taken in into urine concentrations based on the urinary excretion fraction, f_{UE}, of the chemical. Following Angerer et al.[40] the creatinine corrected chemical content in urine, $C_{\mathrm{Cr}}\ (\mathrm{mg}_{\mathrm{intake}}\ \mathrm{mg}^{-1}_{\mathrm{excreted}})$, can be estimated as

$$C_{\mathrm{Cr}} = \frac{I \times BW \times f_{\mathrm{UE}}}{Cr_{24\mathrm{h}}} \qquad (3)$$

where Cr_{24h} ($mg_{excreted}\ d^{-1}$) is the daily creatinine excretion rate. There is very limited data on f_{UE} for parabens available in the literature.[41] Thus, we estimated f_{UE} values based on measured *in vitro* renal and hepatic clearance rates.[42,43] Uncertainty in f_{UE} was included in the analysis by setting upper and lower bounds and running two sets of MC calculations using these high and low bounds of f_{UE} (see SI, Section S5). We also added f_{UE} and Cr_{24h} from Eq. (3) to the Monte Carlo analysis to account for population variability in these parameters. For further details on f_{UE} see SI, Section S5. Eq. (3) was applied to each of the four paraben aggregate intake distributions to yield distributions for paraben urinary concentrations. The percentiles from these distributions can then be compared to the population based urinary concentration percentiles available from NHANES (50th, 75th, 90th, and 95th percentiles for the years 2009-2010).[21]

3. Results

3.1 Paraben Product Intake Fraction

The median product intake fraction during the use-stage, PiF^{use} ranged from 2-88% (2.5th-97.5th percentiles ranged from 0.1-99%) across the product-chemical combinations, with the highest PiF^{use} for EtP in body lotion and the lowest for EtP in conditioner (Figure 1). This indicates that a substantial fraction of the parabens in cosmetics penetrates the skin (Figure S2). In contrast, the mean environmentally mediated PiF^{disp} was three to four orders of magnitude lower than PiF^{use} for all product-chemical combinations, ranging from $10^{-4} – 10^{-3}$ % with the highest PiF^{disp} for PrP in shampoo and the lowest for EtP in body lotion. This implies that the focus can be on the use-stage exposure, which is substantially higher than environmentally mediated exposure, such that the disposal-stage was subsequently excluded from the Monte Carlo analysis. Within the use-stage, dermal aqueous uptake accounted for 78-99% of the total

PiF^{use} indicating that exposure to parabens in PCPs is dominated by direct dermal intake of chemical applied to the skin (Figure S2). As the second main impact pathway, gaseous dermal uptake accounted for 1 to 21% of PiF^{use} and inhalation represented only 0.1 to 1% of PiF^{use}. Weschler and Nazaroff[44] also found that dermal gaseous uptake exceeds the inhalation pathway for parabens.

The large range in PiF^{use} for parabens is mostly due to the variation in the application duration of each PCP; PiF^{use} ranged from 6-50% for rinse-off products with a mean application duration of 4 minutes, and from 50-80% for leave-on products with a mean application duration of 14 hours. A plot of $PiF^{derm,aq}$ versus time (Figure S3a) for the mean product thickness, h (0.01 cm), shows that at 4 minutes (0.07 h), chemical uptake is still in the linear phase of the exponential (with $PiF^{derm,aq}$ ranging from 0.2 – 0.4), whereas at 14 hours, uptake has reached its plateau. For parabens this plateau occurs for $PiF^{derm,aq}$ at or above 80% at the mean product thickness indicating that parabens are readily absorbed into the skin, which has been observed empirically,[32,45] whereas this plateau may occur at a substantially lower $PiF^{derm,aq}$ for more volatile chemicals. This observation is in-line with Gouin et al.[46] who suggested that wash-off products (as opposed to leave-on products) are likely the dominant source of PCP chemicals to WWTPs, noting that this depends on physicochemical properties. For a given chemical, increasing product thickness can also reduce the fractional aqueous uptake (although not necessarily the overall intake via this pathway); thus body wash (mean h = 0.003 cm) had a larger $PiF^{derm,aq}$ than shampoo (mean h = 0.03 cm) (Figure 1) while both are rinse-off products (this is demonstrated in a plot of $PiF^{derm,aq}$ versus time using the product thickness for body wash and shampoo (Figure S3b)). Overall, mean product thicknesses ranged from 10^{-4} (body lotion) to 10^{-2} (shampoo) and are a function of the surface area of the application area and amount of

product applied (Table S1). The $PiF^{derm,aq}$ was more sensitive to product thickness for rinse-off products as the uptake plateau is reached at 8 hours irrespective of leave-on product thickness (Figure S3b).

3.2 Population level paraben intakes

Figure 2 presents the relationship between the potential doses of chemical used (assuming 100% product usage in the population and 100% paraben occurrence) and the effective chemical intake after the indicated adjustment (i.e. product usage, paraben occurrence, and PiF) to the previous adjustment. Adjusting for product usage reduced the potential dose by a factor of 1.4 for the four parabens on average, and the subsequent adjustment for paraben occurrence reduced the potential dose by a factor 1.5 for MeP up to a factor 6 for BuP. Multiplying the effectively applied dose (i.e. after adjusting for product usage and occurrence) by the PiF reduced the population exposure by 3, 1.5, 4, and 2 times for MeP, EtP, PrP, and BuP, respectively. Overall, the final adjusted intakes were 7, 11, 13 and 20 times lower than the potential dose for MeP, EtP, PrP, and BuP, respectively. Cowan-Ellsberry and Robison[1] also found that applying these refinements substantially reduced the population exposure of parabens in PCPs with reductions ranging from a factor 2 to 12.5. Using PrP as an example, body wash, shampoo, body lotion, and conditioner contributed most to the potential applied dose (26, 22, 18, and18%). Once the refinements were applied, body lotion and body wash dominated the total intake (38% and 28%, respectively), whereas shampoo and conditioner combined made up only 13% of the total intake due to lower exposure duration and PiF (Figure 2).

Accounting for product co-use yielded the final modeled exposure distributions for the four parabens (Figure 3). Based on these distributions ~100, 75, 97, and 69% of the adult female population is exposed (i.e. with non-zero intakes) to MeP, EtP, PrP, and BuP, respectively which

compares well to 99, 42, 93, and 47% detection reported for all urine samples (i.e. representing the entire population) from NHANES[22] (Figure S5, SI). The higher detection frequency we determined for female adults are consistent with the highest NHANES paraben urine concentrations for female adults compared to other population groups. MeP and PrP had the highest probability of exposure out of the four parabens (Figure 3), due to their higher frequency of occurrence, while the modeled EtP and BuP intakes were strongly reduced when considering occurrence (Figure 3).

The mean (2.5^{th}-97.5^{th} percentile) modeled population intakes were 0.2 (3×10^{-3}-0.8), 0.03 (0-0.2), 0.06 (0-0.3), 0.02 (0-0.1) mg kg^{-1} d^{-1} for MeP, EtP, PrP, and BuP, respectively (Table 2). These modeled mean intakes fall in-between those found by Cowan-Ellsberry and Robison[1] and Guo and Kannan[12] for paraben exposure due to PCPs (Table S9), noting that these studies did not take population variability into account.

Since some consumers may indeed use all PCP types which may all contain a given paraben, we calculated a high-end intake without applying the exposure adjustments for population exposure (i.e. we did not adjust for product usage, paraben occurrence, and co-use), yielding doses of 8, 3, 4, and 2 mg kg^{-1} d^{-1} for MeP, EtP, PrP, and BuP respectively and are approximately an order of magnitude larger than the 99^{th} percentile stochastically based adjusted exposure estimates. While these high-end estimates of exposures may not necessarily be likely, they may be possible and provide upper end conservative exposure estimates.

3.3 Conversion to biomonitoring levels and comparison to NHANES

Combining urinary excretion rates with the modeled intakes (with all adjustments, i.e. product usage, paraben occurrence, and PiF^{tot}) allows for conversion to urinary concentration distributions, which can be directly compared to the 50^{th}, 75^{th}, 90^{th}, and 95^{th} percentiles of the

NHANES biomonitoring data. Modeled urine concentration percentiles reflect well the NHANES variation of three orders of magnitude across parabens and percentiles and were well correlated ($R^2 = 0.9$ comparing the log). Modeled values were within a factor of three (except for one value) using the *in vitro* estimated values of f_{UE}. When taking uncertainty into account, all modeled values were in agreement with NHANES values (Figure 4). As discussed above, the effect of applying the PiF^{tot} reduced the product usage and paraben occurrence adjusted intakes on average by a factor of 1.5 to 4 (Figure 2) which is a reflection of the median PiF^{tot} being larger than 50% for the majority of the products (i.e the leave-on products). This indicates that the three orders of magnitude variation in the biomonitoring data is not only a function of the PiF but also population variability and the other included exposure adjustments. The comparison to biomonitoring data suggests that the estimated PiFs for parabens are within an order of magnitude of actual intake fractions.

4. Discussion

The PiF is a useful metric to compare product specific chemical intake due to various near- and far-field exposure pathways and routes due to PCP use, and for differentiating exposure between leave-on and rinse-off products instead of assuming a fixed fraction of chemical absorbed into the skin, which may lead to overestimates of the exposure. For parabens, model results suggested that dermal aqueous and gaseous uptake were the dominant exposure pathways and the inhalation and far-field pathways were substantially lower in comparison. Gouin et al. (2013) suggested that the use-phase of PCPs may be used to estimate down-the-drain emissions of PCP chemicals and the framework presented here can also be applied in this context. Furthermore, the PiF for PCPs has an analytical solution and can be calculated based on physicochemical properties and product usage characteristics and thus lends itself to rapid

computational exposure estimates. While this study applied stochastic techniques in-line with Tier 2 exposure calculations[18] to facilitate comparison with bioactivity data, the PiF modeling framework for PCPs can also be readily applied in Tier 1 screening assessments as recommended by Shin et al.[6]

Other exposure media for parabens include food and dust[19,38,39], however these sources have been previously found substantially lower than PCPs.[1,12,39] Soni et al.[19] estimated that the highest likely food intake for MeP and PrP is 0.01 mg kg^{-1} d^{-1} (1 mg d^{-1} normalized to 75 kg used in this study), which is 20 and 6 times lower than our modeled mean intake due to PCP usage for MeP and PrP, respectively. The 95th percentile food intake for the four parabens ranged from 10^{-4}-10^{-6} mg kg^{-1} d^{-1} based on measured food concentrations of parabens in U.S.[39] Intake of the four parabens via dust based on measured dust concentrations was estimated to range between 10^{-6}-10^{-9} mg kg^{-1} d^{-1} [38] and is several orders of magnitude lower than modeled PCP intakes.

To predict paraben intake accurately, it is crucial to account for product usage, paraben occurrence within products, and population variability. Accounting for these exposure adjustments and using modeled PiF for parabens in PCPs yielded agreement between modeled and NHANES urine concentrations. This indicates that a detailed exposure calculation taking into account the chemical and product dependent PiF, exposure probability, and population variability can be an effective method to predict population level chemical intake associated with PCPs.

Uncertainty on the fraction urinary excretion, f_{UE}, is considerable when converting chemical intakes and the limited empirical data available in the literature for parabens resulted in high uncertainty in estimated urine concentrations. Physicochemical property based estimates of pharmacokinetic parameters have recently been made available[42,47] and may be useful for

365 comparing exposure with high-throughput toxicity data for a larger number of chemicals. While
366 the mean modeled urine levels overestimate those of NHANES the R^2 of 0.87 for the log fit of
367 modeled versus measured indicates that the modeling approach presented here was able to
368 capture the exposure patterns of the four parabens well.

369 An additional challenge when estimating aggregate exposure is to effectively take into
370 account product co-use.[1] While several PCP usage studies report some data on product co-use,
371 this information cannot be practically applied to a comprehensive PCP study as the data
372 presentation is often incomplete; for example, only the most commonly used combinations, the
373 correlation between the use of two products (rather than multiple products), or data on different
374 sets of PCPs are presented,[1,48,49] and certain PCPs of interest are not included in that dataset. By
375 accounting for the probability of using a product, we were able to provide an initial reasonable
376 estimate of product co-use, which could be complemented by multiple product usage conditional
377 probabilities. Furthermore, co-use becomes even more complex when chemicals occur in
378 different product types, for example PCPs and cleaning products and alternative methods for
379 taking co-use into account may be needed.

380 Within the context of risk screening, the exposure refinements needed for a population
381 level calculation may not necessarily be needed to calculate exposure for high-end product users
382 (for example, those who use several PCPs with high-end product masses within the intended
383 product usage) to protect all users rather than an average user. For example, exposure estimates
384 can be compared with the allowable daily intake (ADI) to inform risk of parabens in PCPs.
385 While there is no ADI for EtP and BuP, the combined ADI for MeP and PrP in the European
386 Union is 0-10 mg kg^{-1} d^{-1} [19,23] which is within an order of magnitude of both the high-end user

combined intake of 12 mg kg^{-1} d^{-1} and the 99^{th} percentile stochastically estimated intake (with exposure adjustments) of 1.5 mg kg^{-1} d^{-1}.

We presented a detailed population level PCP exposure model which is able to predict the three orders of magnitude of variation in NHANES paraben urine concentrations. The PCP product intake fraction model can be readily incorporated into rapid exposure models and can be combined with concentration databases such as the recently released Consumer Product Chemical Profile database CPCPdb[26] to estimate chemical intakes due to PCP use.

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547 **Tables**

	MeP	EtP	PrP	BuP	Notes and Reference
$logK_{aw}$	-5.6	-6.0	-5.2	-4.9	Calculated from solubility and vapor pressure, EPI Suite [50]. Values listed here are at 25 ºC and were corrected to skin temperature of 32 ºC for use in the model (see Sec. S.1).
K_p^{aq} (cm h^{-1}) (geometric mean, GSD^2)	0.012, 31	0.009, 19	0.009, 31	0.023, 31	Lognormal distribution. See Table S3[a]
K_p^{gas} (cm h^{-1}) (geometric mean, GSD^2)	4200, 28	10000, 28	1400, 28	1800, 28	Lognormal distribution. Geometric mean calculated using equation in Table S1. GSD^2 was set to the mean of K_p^{aq} GSD^2.Values are at 25ºC and were corrected to skin temperature.
f_p shampoo (%) (low – high)	0.01 to 0.2	0 to 2×10^{-4}	1×10^{-3} to 0.2	2×10^{-4} to 0.045	Uniform distribution. See Table S4[b]
f_p body lotion (%) (low – high)	0.01 to 0.29	0.01 to 0.2	0.01 to 0.2	0 to 0.085	Uniform distribution. See Table S4[b]
f_p range for all products % (low – high)	8×10^{-6} to 0.5	0 to 0.35	0 to 0.28	0 to 0.27	Uniform distribution. See Table S4[b]
M_p shampoo (g d^{-1}) (2.5^{th} -97.5^{th} percentile)	1.7 to 34				Gamma distribution. [35]
M_p body lotion (g d^{-1}) (2.5^{th} -97.5^{th} percentile)	2.5 to 21				Gamma distribution. [34]
M_p range for all products (g d^{-1})	8×10^{-4} to 44 (Min 2.5^{th} – max 97.5^{th} percentile)				[34–36]. See Figure S1

548 **Table 1:** Summary input data for main model parameters for methyl, ethyl, propyl, and butyl
549 paraben. Further information and input data can be found in the SI. Notes: [a]See Table S3 for
550 references. [b]Based on data from [1,12,37]. GSD^2 = geometric standard deviation squared.

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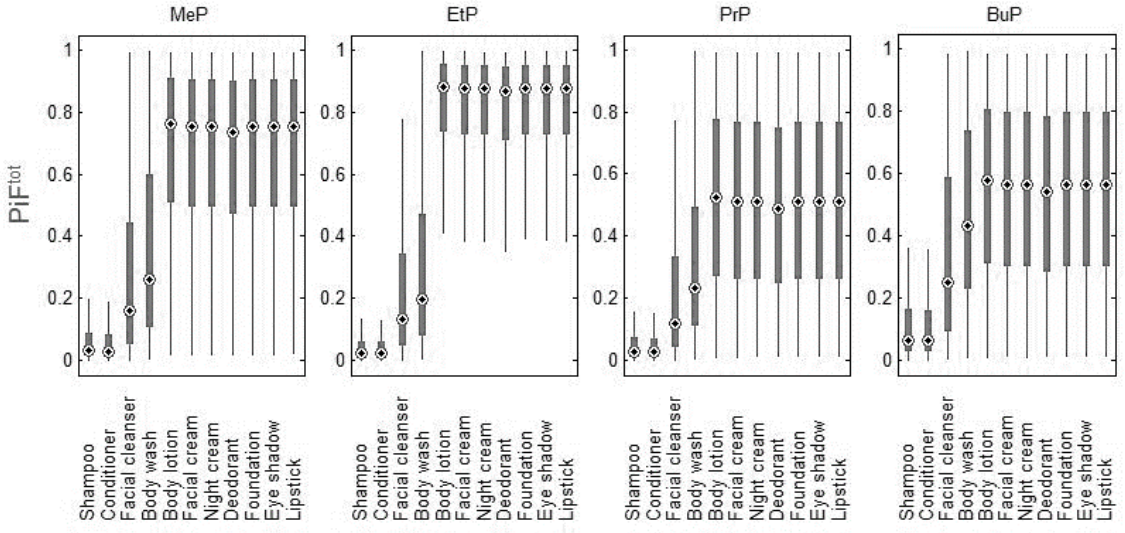
554 **Figures**



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556 **Figure 1:** Modeled total product intake fraction (PiF^{tot}) for the 11 personal care products for
557 MeP, EtP, PrP, and BuP (from left to right). The circles represent the median, the solid boxes
558 represent the 25th and 75th percentiles, and the lines represent the 2.5th and 97.5th percentiles of
559 PiF^{tot} calculated using Monte Carlo simulation.

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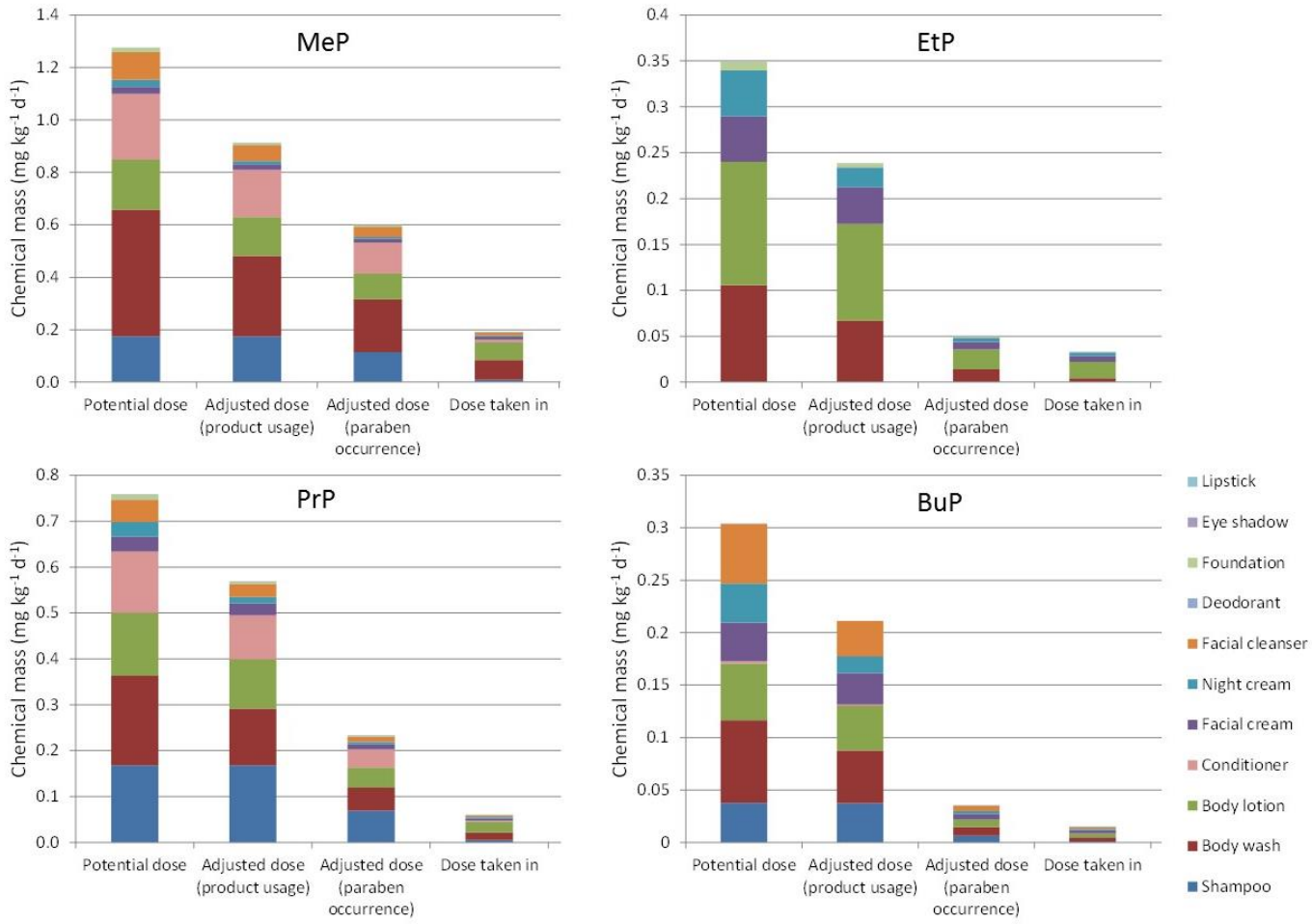

Figure 2: Reduction in potential applied chemical dose due to population PCP usage, paraben occurrence in products, and product intake fraction to yield the mean dose taken in for each product-chemical combination calculated by Monte Carlo simulations. The reductions were applied sequentially, thus the last column represents the dose based on all three reductions.

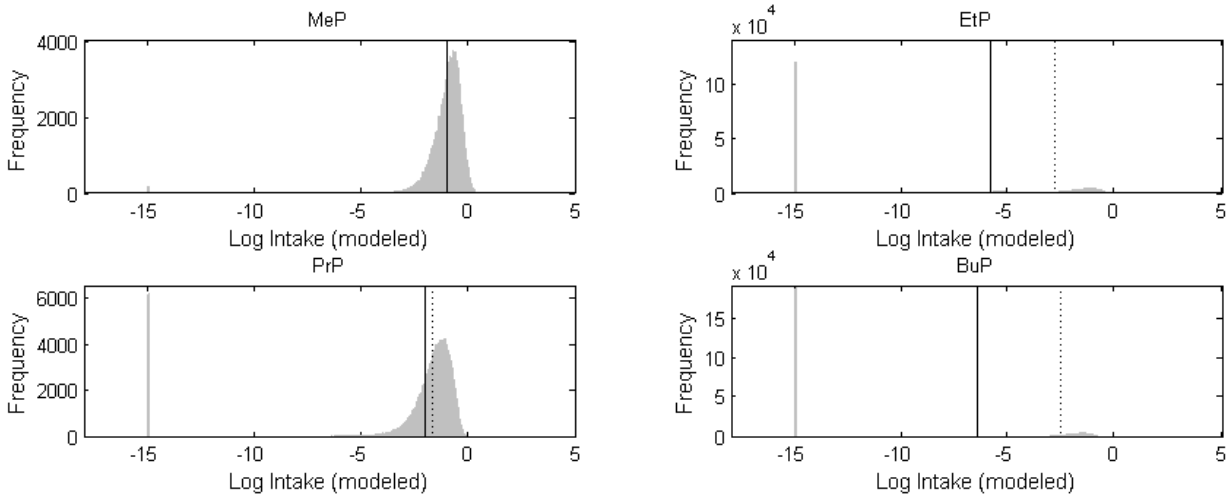

Figure 3: Modeled log intake (mg kg d^{-1}) distributions for the four parabens taking into account probability of exposure and product co-use. The grey solid vertical lines indicate the population with zero exposure (zero intakes were adjusted to a nominally low value (1×10^{-15}) to make them visible on a log scale). The dashed line indicates the geometric mean of the exposed population and the black solid line indicates the geometric mean of the entire population (with adjusted zero intakes).

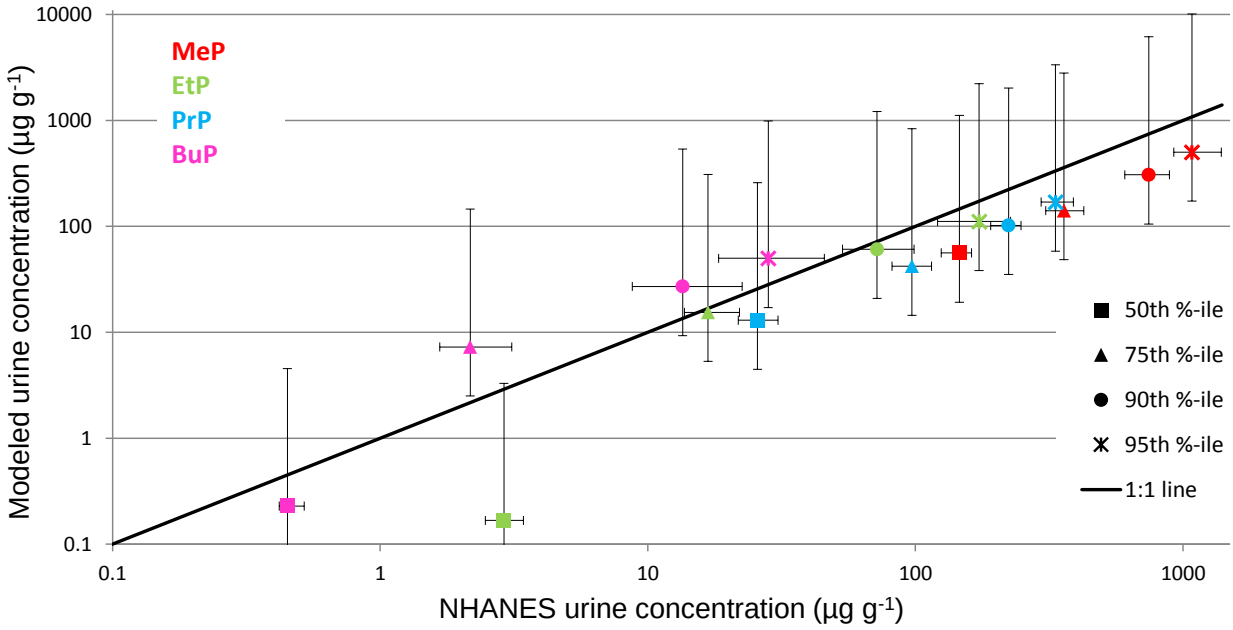

Figure 4: Modeled urine concentrations from the Monte Carlo calculations versus NHANES urine concentrations. Vertical error bars on the modeled values represent uncertainty in fraction urinary excretion and horizontal error bars on the NHANES values represent the 95th confidence interval on each percentile. The solid line indicates perfect agreement between modeled and measured values (1:1 line).